REMARKS

Reconsideration of the Office Action mailed February 3, 2003, (hereinafter "instant Office Action"), entry of the foregoing amendment and withdrawal of the rejection of claims 1-13, 15-25 and 27-29, are respectfully requested.

In the instant Office Action, claims 1-13, 15-25 and 27-29 are listed as pending, and claims 1-13, 15-25 and 27-29 are listed as rejected.

Attached hereto as Appendix A is a marked-up version of the changes made to the claims by the current amendments. Appendix A is captioned **"Version with markings to show changes made"**.

The Examiner has rejected claims 1-13, 15-25 and 27-29 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for inhibiting vascular hyperpermeability using the compound disclosed on page 33 of the specification, allegedly "does not reasonably provide enablement for all other known and unknown (to be developed in the future) compounds". Applicants respectfully traverse this rejection. The Examiner further alleges that the instant specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims based on the quantity of experimentation necessary, the amount of direction or guidance provided, presence or absence of working examples and the state of the prior art.

The present invention is directed to the use of a compound that inhibits the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases to inhibit vascular hyperpermeability. The present invention is not directed to the discovery or making of such a compound. Accordingly, an inherent requirement of the claim is to identify a compound as having the ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR01 or other kinases. Applicants have provided assays on pages 25-36 of the instant application that enable the identification of such compounds.

With respect to the Examiner's allegation that undue experimentation is required to use the instant invention, the determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc., 4 F.2d 872 (2d

Cir. 1971). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. In re Rainer, 52 CCPA 1593, 347 F.2d 574, 146 USPQ 218 (1965); In re Colonianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

The instant specification teaches assays used to identify compounds with the ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases compounds of the invention are described on pages 25-36 of the instant application, as the Examiner has acknowledged. The assays are well known to those skilled in the art, as evidenced by the instant detailed disclosure and are enabled by the reference cited (see page 32, line 10 of the published PCT application). The amount of experimentation required to utilize the instant invention is routine in the field of medicinal chemistry, and, thus, is not undue.

With respect to the Examiner's allegation that the specification is not enabling based on the presence or absence of working examples provided in the instant specification, Applicants direct the Examiner's attention to the table on page 34 of the corresponding published PCT application, WO00/27414, which lists results demonstrating the inhibitory activity of the compounds of the instant invention for KDR tyrosine kinase activity. As stated in M.P.E.P. 2164.01(b), as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Applicants respectfully point out that there is no requirement as to how many working examples must be provided in a patent application. Further, the Court of Customs and Patent Appeals (CCPA), which has now been superseded by the Court of Appeals for the Federal Circuit, stated in In re Borkowski, 164 U.S.P.Q. 642 (C.C.P.A. 1970) that

"[T]here is no magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated.'" Id. at 646. Applicants have submitted an enabling disclosure including the use of the compound disclosed on page 33 of the instant application, which is believed to be the 'best mode'." Furthermore, the CCPA has stated that the specification need not contain a working example of every embodiment of the invention "if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it." In re Borkowski, 164 U.S.P.Q. 642, 645 (CCPA 1970). See United States v. Telectronics, Inc., 8 U.S.P.Q. 2d 1217 (Fed. Cir. 1988). The instant specification is enabled and that enablement is evidenced by the fact that the assays described in the instant specification identified a compound with the ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases.

With respect to the Examiner's allegation that the instant specification is not enabling based on the amount of direction or guidance provided, Applicants submit that they have provided the structure of a representative compound used to inhibit VEGF activity and detailed the assays used to measure the inhibitory effects of said compound. Pharmaceutical formulations, routes of administrations, composition/formulation and effective dosage have been described on pages 19-25 of the corresponding published PCT application, WO00/27414. Applicants have clearly enabled others to use the instant invention.

As stated in M.P.E.P. 2164.01:

> "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 662, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

On page 7, lines 10-30 of the instant specification, Applicants list published PCT patent applications, granted U.S. patents and a literature citation which disclose various compounds as kinase inhibitors. One of ordinary skill in the art could test the compounds disclosed in these

references using the assays described in the instant specification to determine whether said compounds can be utilized in the instant invention. Therefore, there is sufficient guidance to identify KDR inhibitors with the ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 and to use such compounds to inhibit vascular hyperpermeability.

With respect to the state of the prior art, Applicants have provided assays to use in determining whether a compound inhibits the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases. The assays provided in the instant specification are within the realm of one of ordinary skill of the art to use to identify compounds that have the desired activity. The example at page 36 in the instant specification was determined using these assays, which are predictable for identifying such compounds.

Based upon the foregoing, the rejection of claims 1-13, 15-25 and 27-29 under 35 U.S.C. §112, first paragraph is obviated and should be withdrawn.

The Examiner has rejected claims 1-13, 15-25 and 27-29 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. The Examiner alleges that the term "a compound that inhibits the cellular signaling function" is indefinite since it is not clear which compound is being referred to. Applicants respectfully traverse this rejection.

Applicants have defined the compounds of the instant invention by the function of the ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases. It is the use of a compound that has the ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases that results in the inhibition of vascular hyperpermeability, which is the invention of the instant application. M.P.E.P. 2173.05(g) states:

> A functional limitation is an attempt to define something by what it does, rather than what it is (e.g. as evidenced by its specific structure or specific ingredients). There is nothing inherently wrong with defining some part of an invention in functional terms.

The question of whether compounds can be defined by functional limitations was examined in In re Barr, 444 F.2d 588, 170 USPQ (BNA) 330, (CCPA 1971). In In re Barr, claim 23 read upon a photographic color coupler having the formula COUP-S-R

wherein R is an organic radical incapable of forming a dye with said oxidized developing agent and being selected from the group consisting of an alkyl radical, a cycloalkane radical, an aryl radical and a heterocyclic radical containing at least one hetero atom selected from the group consisting of oxygen, sulfur and nitrogen.

The gist of the principal rejection in In re Barr, as expressed by the examiner, is that the claims "appear to read on vast numbers of compounds" and that the Applicants failed "to point out what applicants regard as their invention with the specificity required by 35 U.S.C. 112". Additionally, the examiner held that the phrase "incapable of forming a dye with said oxidized developing agent" is "unduly functional at a point of novelty".

The Board of Appeals affirmed the Examiner's rejection of the claim on the ground that the limitation "incapable of forming a dye with said oxidized developing agent" placed on the organic radical R is "negative and functional". However, the CCPA held:

> that an applicant may invoke the third paragraph of section 112 to justify the specification of one or more elements of a claimed compound in "functional" terms, and that those "functional" terms may be "negative". The real issue in such case is not whether the recital is "functional" or "negative" but whether the recital sets definite boundaries on the patent protection sought – that is, whether those skilled in the relevant art can determine what the claim does or does not read on. Judged by this standard, we think it clear that the controverted language complies with the second paragraph of section 112.

Although the phrase in question in In re Barr referred to an organic radical selected from a set of radicals and the phrase in question in the instant application refers to a compound, the issue is essentially the same. Applicants have defined the compound that is used in claims 1-13, 15-25 and 27-29 by a function, namely its ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases. Furthermore, Applicants have provided the assays necessary to test kinase inhibitors to determine whether the claims read on kinase inhibitors with the ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases. Therefore, Applicants have clearly and definitely defined which compounds these claims read on.

Based upon the foregoing, the rejection of claims 1-13, 15-25 and 27-29 under 35 U.S.C. §112, second paragraph, is obviated and should be withdrawn.

The Examiner has rejected claims 1-13, 15-25 and 27-29 under 35 U.S.C. §102(e) for allegedly being anticipated by Arnold et al. (U.S. Patent no. 6,451,834). The Examiner alleges that Arnold et al. discloses compounds as inhibitors of tyrosine kinase activity having utility for inhibiting vascular hyperpermeability. Applicants respectfully traverse this rejection.

In the instant application, after entry of the amendments hereinabove, the method inhibits vascular hyperpermeability by inhibiting the cellular signaling function of KDR by disrupting the catalytic kinase response of KDR/VEGFR-2 without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases. Support for this amendment can be found on page 9, lines 9-11 of the instant specification. In the instant invention, the method selectively inhibits the cellular signaling function of KDR. Arnold et al., on the other hand, discloses compounds that inhibit the activity of the KDR/FLK-1/VEGFR-2 tyrosine kinases and may also inhibit the activity of other tyrosine kinases, such as Flt-1/VEGFR-1, Src-subfamily kinases such as Lck, Src, Fyn and yes. Arnold et al. does not teach the use of compounds with the ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases for inhibiting vascular hyperpermeability.

Based upon the foregoing, the rejection of claims 1-13, 15-25 and 27-29 under 35 U.S.C. §102(e) for allegedly being anticipated by Arnold et al. (U.S. Patent no. 6,451,834) is obviated and should be withdrawn.

The Examiner has rejected claims 1-13, 15-25 and 27-29 under 35 U.S.C. §102(e) for allegedly being anticipated by Doyle (U.S. Patent no. 6,297,238). Applicants respectfully traverse this rejection. The instant application claims priority to U.S. Provisional Patent Application No. 60/107,462, filed November 6, 1998. Doyle claims priority to U.S. Provisional Patent Application No. 60/127,963, filed April 6, 1999. The instant application predates Doyle by a full six months and therefore, Doyle is not available as a 102(e) reference against the instant application.

Based upon the foregoing, the rejection of claims 1-13, 15-25 and 27-29 under 35 U.S.C. §102(e) for allegedly being anticipated by Doyle (U.S. Patent no. 6,297,238) is obviated and should be withdrawn.

No fees are due for the instant amendment since the total number of claims after entry of the amendments hereinabove is not more than the total number of claims that Applicants have paid for to date.

Based upon the foregoing, Applicants believe that claims 1-13, 15-25 and 27-29 are in condition for allowance. Prompt and favorable action is earnestly solicited.

If the Examiner believes that a telephone conference would advance the condition of the instant application for allowance, Applicants invite the Examiner to call Applicants' agent at the number noted below.

Respectfully submitted,

Date: June 3, 2003

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice Amended) A method of inhibiting vascular hyperpermeability in an individual comprising the step of administering to said individual a therapeutically effective amount of a compound that inhibits the cellular signaling function of KDR by disrupting the catalytic kinase response of KDR/VEGFR-2 without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases.